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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/533,838	05/04/2005	William Brown	100885-1P US	6088
22466 7590 07/10/2007 ASTRA ZENECA PHARMACEUTICALS LP GLOBAL INTELLECTUAL PROPERTY 1800 CONCORD PIKE WILMINGTON, DE 19850-5437			EXAMINER ROBINSON, BINTA M	
			ART UNIT 1625	PAPER NUMBER
			MAIL DATE 07/10/2007	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/533,838	BROWN ET AL.	
	Examiner	Art Unit	
	Binta M. Robinson	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-11 and 14-23 is/are pending in the application.
- 4a) Of the above claim(s) 14-17 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-11 and 18-23 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|--|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>1/9/06</u> . | 6) <input type="checkbox"/> Other: ____ |

DETAILED ACTION

Election/Restrictions

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions, which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1-11 and 18-23, drawn to the compounds and process of preparing these compounds.

Group II, claim(s) 14-17, drawn to the uses of the compounds.

The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Group I and II are linked by the technical feature of compound of formula I. However, as evidenced by WO 9828275, compound of formula I does not make a contribution over the prior art and does not link the product and method claims into a single general inventive concept. If applicants elect the product and if it is found free of the prior art, the method claims may be eligible for rejoinder practice under 821.04(b).

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The species are as follows:

The species in claim 11 and compounds 1 through 54 in the specification pages 39 through 76.

Applicant is required, in reply to this action, to elect a single species to which the claims shall be restricted if no generic claim is finally held to be allowable. The reply

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must also identify the claims readable on the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

The following claim(s) are generic: 1-10, 14-23.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: the species lack a common core.

During a telephone conversation with Jennifer Cohen on 5/8/07, she elected with traverse to prosecute the invention of Group I, claims 1-11, 18-23. Affirmation of this election must be made by applicant in replying to this Office action. Claims 14-17 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. The species of compound 18 was elected.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Advisory of Rejoinder

The following is a recitation of M.P.E.P. §821.04, Rejoinder:

Where product and process claims drawn to independent and distinct inventions are presented in the same application, applicant may be called upon under 35 U.S.C. 121 to elect claims to either the product or process. See MPEP § 806.05(f) and § 806.05(h). The claims to the nonelected invention will be withdrawn from further consideration under 37 CFR 1.142. See MPEP § 809.02© and § 821 through § 821.03. However, if applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims which depend from or otherwise include all the limitations of the allowable product claim will be rejoined.

Where product and process claims are presented in a single application and that application qualifies under the transitional restriction practice pursuant to 37 CFR 1.129(b), applicant may either (1) elect the invention to be searched and examined and pay the fee set forth in 37 CFR 1.17(s) and have the additional inventions searched and examined under 37 CFR 1.129(b)(2), or (2) elect the invention to be searched and examined and not pay the additional fee (37 CFR 1.129(b)(3)). Where no additional fee is paid, if the elected invention is directed to the product and the claims directed to the product are subsequently found patentable, process claims which either depend from or include all the limitations of the allowable product will be rejoined. If applicant chooses to pay the fees to have the additional inventions searched and examined pursuant to 37 CFR 1.129(b)(2), even if the product is found allowable, applicant would not be entitled to a refund of the fees paid under 37 CFR 1.129(b) by arguing that the process claims could have been rejoined. 37 CFR 1.26 states that "[m]oney paid by actual mistake or in excess will be refunded, but a mere change of purpose after the payment of money...will not entitle a party to demand such a return..." The fees paid under 37 CFR 1.129(b) were not paid by actual mistake nor paid in excess, therefore, applicant would not be entitled to a refund.

In the event of rejoinder, the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104 - 1.106. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. If the application containing the rejoined claims is not in condition for allowance, the subsequent Office action may be made final, or, if the application was already under final rejection, the next Office action may be an advisory action.

The following is a recitation from paragraph five, "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai*, *In re Brouwer* and 35 U.S.C. §103(b)" (1184 TMOG 86(March 26, 1996)):

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“However, in the case of an elected product claim, rejoinder will be permitted when a product claim is found allowable and the withdrawn process claim **depends from or otherwise includes all the limitations of** an allowed product claim. Withdrawn process claims not commensurate in scope with an allowed product claim will not be rejoined.” (emphasis added)

Therefore, in accordance with M.P.E.P. §821.04 and *In re Ochiai*, 71 F.3d 1565, 37 USPQ 1127 (Fed. Cir. 1995), rejoinder of product claims with process claims commensurate in scope with the allowed product claims will occur following a finding that the product claims are allowable. Until, such time, a restriction between product claims and process claims is deemed proper. Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution to maintain either dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

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Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-2, are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 8 of copending Application No. 20070099957. Although the conflicting claims are not identical, they are not patentably distinct from each other because '957 discloses a genus of compounds, which are positional isomers of the instant genus of compounds.

'957 teaches the compound as shown in Formula IA, wherein R1 is hydrogen, C1-6alkyl-O-C(O), C1-6alkyl, C3-6cycloalkyl, wherein said C1-6alkyl, C3-6cycloalkyl are optionally substituted with one or more groups selected from R, NO₂, OR, Br, I, F, CF₃, and R is C1-6 alkyl, R4 is C1-6 alkyl or C3-6 cycloalkyl, R7 is H or C1-6 alkyl. At page 41, column 1, see the radicals defined. The difference between the prior art compound and the instantly claimed compounds is the teaching of a genus of compounds, which are positional isomers of the instant genus of compounds. The NR₄(R₇) moiety on the '457 compound is at the 2 position whereas in the instant compound, the analogous group which is NR₂R₁ is at the 3 position. It would have been obvious to one of ordinary skill in the art to select various known radicals within a genus to prepare structurally similar compounds. The '457 compounds are useful in therapy and thus it would have been obvious to modify the '457 compounds to the instant compounds which are positional isomers. Accordingly, the compounds are deemed unpatentable therefrom in the absence of a showing of unexpected results for the claimed compounds over those of the generic prior art compounds.

Claims 11 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 5 of copending Application No. 20070099957. Although the conflicting claims are not identical, they are not patentably distinct from each other because '957 discloses compounds which are positional isomers of the instant compounds.

'957 teaches the compounds in claim 5. At page 52, columns 1-2, see the '957 compounds. The difference between the prior art compound and the instantly claimed compounds is the teaching of compounds, which are positional isomers of the instant compounds. The NR₄(R₇) moiety on the '457 compound is at the 2 position whereas in the instant compound, the analogous group which is NR₂R₁ is at the 3 position. It would have been obvious to one of ordinary skill in the art to select various known radicals within a genus to prepare structurally similar compounds. The '457 compounds are useful in therapy and thus it would have been obvious to modify the '457 compounds to the instant compounds which are positional isomers. Accordingly, the compounds are deemed unpatentable therefrom in the absence of a showing of unexpected results for the claimed compounds over those of the generic prior art compounds.

Claims 1-2 and 11 are directed to an invention not patentably distinct from claims 1-5 and 8 of commonly assigned application 10555980. Specifically, this application teaches '957 teaches the instant compound as shown in Formula IA, wherein R₁ is hydrogen, C₁-6alkyl-O-C(O), C₁-6alkyl, C₃-6cycloalkyl, wherein said C₁-6alkyl, C₃-6cycloalkyl are optionally substituted with one or more groups selected from R, NO₂,

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OR, Br, I, F, CF₃, and R is C1-6 alkyl, R₄ is C1-6 alkyl or C3-6 cycloalkyl, R₇ is H or C1-6 alkyl as well as specific compound species. At page 41, column 1, see the radicals defined and at claim 5, see the compound species. The difference between the prior art compound and the instantly claimed compounds is the teaching of a genus of compounds which are positional isomers of the instant genus of compounds and species which are positional isomers of the instant species. The NR₄(R₇) moiety on the '457 compound is at the 2 position whereas in the instant compound, the analogous group which is NR₂R₁ is at the 3 position. It would have been obvious to one of ordinary skill in the art to select various known radicals within a genus to prepare structurally similar compounds. The '457 compounds are useful in therapy and thus it would have been obvious to modify the '457 compounds to the instant compounds which are positional isomers. Accordingly, the compounds are deemed unpatentable therefrom in the absence of a showing of unexpected results for the claimed compounds over those of the generic prior art compounds.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-10 and 18-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. In claim 1, line 2, and everywhere else throughout the claims, the phrase "diastereomers, enantiomers, or mixtures thereof" is indefinite. A compound species is claimed, and with the phrase referring to diastereomers and enantiomers in the plural

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and referring to mixtures – it is unclear if a compound is being claimed or a pharmaceutical composition.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10, 18-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using the compounds of formula I with R1 equal to benzylaminocarbonyl, cyclopentyl, phenyl, cycloheptanyl, , 2-chlorobenzoyl, 3-chlorobenzoyl, benzyl, 3-methylfuranyl, cyclohexyl, ethyl, 5-methylthien-2-yl)acetyl, 5-chlorothien-2-ylacetyl, 2-phenylpropanoyl, 2-phenylbutanoyl, benzoyl, anilincarbonyl, piperidinecarbonyl, piperidinylmethylsulfonyl, phenylethyl, cyclohexylethyl, dipropylcarbonyl, 1 , 2, 3-benzotriazolecarbonyl; 1-methyl, 1,2, 3-benzotriazolecarbonyl, 3-pyridinecarbonyl, 2-methoxyphenylcarbonyl, 2-quinoxalinecarbonyl, 2,5-difluorophenylcarbonyl, 2-thiophenecarbonyl, methylphenylaminocarbonyl and wherein R1 and R2 come together to form a piperidine ring or pyrrolidine ring, R3 equal to hydrogen, and R2 equal to H, methyl, and ethyl, does not reasonably provide enablement for using the compounds of formula I where R1, R2, and R3 equal to any of the other moieties claimed. The specification does not enable any

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skilled pharmacologist or physician to use the invention commensurate in scope with these claims. The factors to be considered in making an enablement rejection have been summarized above.

a) Determining if any particular claimed compounds with R1-R3 equal to any of the other moieties claimed other than those enabled above would be active would require synthesis of the substrate and subjecting it to testing with Applicants' GTP binding assay. Considering the large number of compounds to be made this is a large quantity of experimentation. b) The direction concerning the claimed compounds is found in pages 39-75, which merely states Applicants' intent to make and use such compounds. c) In the instant case none of the working examples contains any radical R1-R3 equal to any of the moieties claimed other than the ones enabled above.

d) The nature of the invention is activity towards the delta opioid receptor and treatment of human diseases with Applicants' compounds. This involves physiological activity. The nature of the invention requires an understanding of the receptor, the binding activity of small ligands to that receptor, and the ability of those compounds to modulate the delta opioid receptor. In view of the unpredictability of receptor binding activity and claimed divergent substituents with varied polarity, size, and polarisability, the skilled physician would indeed

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question the inclusion of such diverse rings, commensurate in scope with these claims. Also see the MPEP § 2164.03 for enablement requirements in the structure sensitive arts of pharmacology and medicinal chemistry.

e) There is no reasonable basis for the assumption that the myriad of compounds embraced by the present formula (I) will all share the same biological properties. For example, a cyclohexyl ring has different chemical properties than a thiophenyl ring. The diverse claimed compounds are chemically non-equivalent and there is no basis in the prior art for assuming in the non-predictable art of pharmacology that structurally dissimilar compounds will have such activity, *In re Surrey* 151 USPQ 724 (compounds actually tested which demonstrated the asserted psychomotor stimulatory and anti-convulsant properties were those having the 3,4-dichlorophenyl substituent at the 2-position on the thiazolidone nucleus not sufficient for enablement of any heterocyclic radical at the same position). *In re Fouché*, 169 USPQ 429 at 434 (a Markush group including both aliphatic and heterocyclic members not enabled for the use of those compounds within the claim having heterocyclic moieties.) *In re CAVALLITO AND GRAY*, 127 USPQ 202 (claims covering several hundred thousand possible compounds, of which only thirty are specifically identified in appellants' application, not enabled unless all of the thirty specific compounds disclosed had equal hypotensive potency because

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that fact would strongly indicate that the potency was derived solely from the basic structural formula common to all of them. A wide variation in such potency would suggest that it was due in part to the added substituents and might be eliminated or even reversed by many of the possible substituents which had not been tried.)

f) The artisan using Applicants' invention to treat diseases with the claimed compounds would be a physician with a MD degree and several years of experience. He would be unaware of how to predict *a priori* how a changing a heterocyclic ring would affect biological activity. In view of the divergent rings with varied basicity, steric hindrance, and polarisability, the skilled physician would indeed question the inclusion of such fused rings, commensurate in scope with these claims. g) Physiological activity, is well-known to be unpredictable, *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). h) The breadth of the claims includes all of millions of compounds of formula (I). Thus, the scope is very broad. The present claims embrace various heterocyclic radicals, which are not art-recognized as equivalent. The specific

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compounds made are not adequately representative of the compounds embraced by the extensive Markush groups instantly claimed.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Delorme. (See Reference N, WO 9828275).

Delorme teaches the compound as shown in Formula I, which is a genus of compounds which overlap in scope with the instant genus of compounds. At pages 103-105, see the compound of formula I in claim 1. The difference between the prior art compound and the instantly claimed compounds is the teaching of a generic compound

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which overlaps in subject matter with the instant genus of compounds. It would have been obvious to one of ordinary skill in the art to select various known radicals within a genus to prepare structurally similar compounds. Accordingly, the compounds are deemed unpatentable therefrom in the absence of a showing of unexpected results for the claimed compounds over those of the generic prior art compounds.

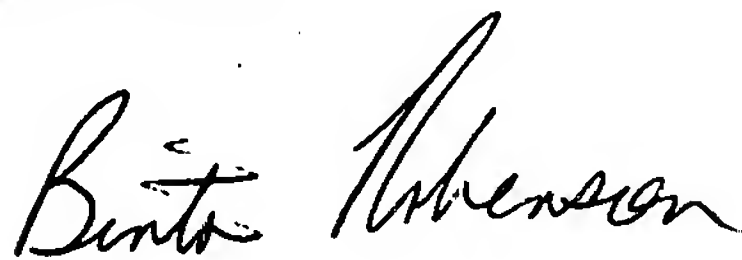
The elected species is not allowable because compound 2 in claim 5 of '957 is a positional isomer of the elected species.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Binta M. Robinson whose telephone number is (571) 272-0692. The examiner can normally be reached on M-F (9:30-6:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Janet Andres can be reached on 571-272-0867.

A facsimile center has been established. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine are (703)308-4242, (703)305-3592, and (703)305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)-272-1600.



BMR
July 5, 2007



JANET L. ANDRES
SUPERVISORY PATENT EXAMINER